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Urorectal Septal Defects in a Female and Her Offspring

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We report on a patient with an ectopic urethra opening into a septate vagina which was distended with urine. The anus and rectum were normal but separated from the urogenital sinus by a thin septum. After surgical repair the patient did well with the exception of recurrent urinary tract infections. At 16 years, she delivered a healthy boy by Cesarean section but miscarried a subsequent pregnancy 3 years later. The 12–13 week female fetus lacked a urethra and had an atretic vagina and cloacal anomalies consistent with a urorectal septum developmental defect. This report provides evidence that cloacal anomalies resulting from the improper development of the urorectal septum may have a genetic cause. Furthermore, we support the proposition previously set forth by Allen and Husmann [J Urol 145:1034-1039, 1991] that such anomalies be referred to as urorectal septal defects rather than cloacal anomaly variants. This terminology accurately represents the developmental defect and clearly distinguishes them from cloacal exstrophies, which are due to the abnormal development of the cloacal membrane and the subumbilical ventral abdominal wall. Am. J. Med. Genet. 70:250–252, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: urogenital sinus; cloacal anomaly; urorectal septal defect

INTRODUCTION

Abnormalities of the cloaca comprise three distinct but related categories: persistent cloaca, persistent urogenital sinus, and exstrophy anomalies [Wood, 1990]. Persistent cloaca and urogenital sinus anomalies affect females; they occur in an estimated 1:50,000 births [Alexander and Kay, 1995]. Exstrophy anomalies affect twice as many males as females and include epispadias (1:120,000 births), bladder exstrophy (1:30,000 births), and cloacal exstrophy (1:400,000 births) [Jeffs, 1987].

A patient with a persistent cloaca has a single perineal orifice for the urinary, reproductive and lower gastrointestinal tracts; communications between these tracts can occur. Müllerian malformations such as atretic, duplicated, or septate organs are often seen in cases of a persistent cloaca. Related complications are urinary tract or bowel obstructions and hydrometrocolpos. Renal anomalies, esophageal or duodenal atresia, congenital heart defects, and spinal cord anomalies have been reported in cases of persistent cloaca [Wood, 1990].

Patients with a persistent urogenital sinus have a common orifice for the urethra and vagina and an enlarged clitoris but a normal anus. The anus can be anteriorly displaced yet functional [Allen and Husmann, 1991]. The urogenital orifice may be obstructed, causing urine and vaginal secretions to be pooled in the Müllerian structures. A severely affected patient can have vaginal atresia usually associated with absence of the kidneys [Wood, 1990].

Exstrophies include anomalies ranging from epispadias (the mildest) to cloacal exstrophy (the most severe). In the classic form of bladder exstrophy, the anterior abdominal wall is open over the dorsal surface of the penis and the bladder neck; the open region extends to the umbilicus and the rectal muscles are widely separated and functionally deficient. The anus is anteriorly displaced and the pubic bones are widely separated. Patients with cloacal exstrophy have bladder exstrophy with a hypoplastic, externalized hindgut that divides bladder and phallus. Duplication of the bladder can occur. A female with cloacal exstrophy can have duplicated Müllerian structures. A patient with cloacal exstrophy lacks an anus. Frequently, these patients will have an omphalocele as well as spinal column and cord anomalies. The term "OEIS" complex has been used to describe patients with Omphalocele, Exstrophy, Imperforate anus, and Spinal defects [Carey et al., 1978]. Cardiovascular and limb defects have also been reported in cases of exstrophy anomalies [Wood, 1990].

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We describe a familial case of cloacal anomalies, discuss the embryogenesis of persistent cloaca, persistent urogenital sinus, and exstrophy defects, and propose that a genetic basis be considered for these rare defects.

CLINICAL REPORTS

Proposita

At birth, this infant girl was noted to have a large lower abdominal mass and a single, small opening just in front of the anus, which itself was slightly anterior to its normal position. A pregnancy history was not available.

At operation, on her first day of life, the mass was found to be the vagina filled with urine. A small perineal opening communicated with the vagina which was divided by a septum. Uterus and ovaries were identified. It was possible to pass probes through bladder and vagina into a common canal and through the stenotic orifice on the perineum. This represented a urogenital canal. Urine drained preferentially into the dilated vagina; therefore both a vaginotomy and a vesicostomy were made by suturing the vagina and the bladder to the skin of the lower abdominal wall.

The patient developed normally during her first year of life, but urine continued to drain from the vaginotomy, whereas the vesicostomy closed spontaneously.

At age 14 months, the patient underwent a second operation. The bladder was again opened to identify each ureter and the urethral opening into the urogenital sinus. A new urethra was constructed over a foley catheter in order to separate the urinary tract from her vagina.

During her first several years of life, the patient experienced urinary incontinence and urinary tract infections.

At 6 years, cystoscopy demonstrated a rather large, "floppy" bladder; a clitoral reduction was performed. By 9 years, complete urinary control was attained with no recurrence of urinary tract infections. At 16 years the patient delivered a reportedly healthy son by Cesarean section. The pregnancy was complicated by recurring urinary tract infections. At 19 years the patient underwent a dilatation and evacuation (D&E) 13 weeks and 2 days after the first day of her last menstrual period, after it was determined that she had a missed abortion. The patient denied teratogenic exposures during this pregnancy. The family medical history was non-contributory.

Fetus

Autopsy of the fetus indicated a 12–13 week female with lack of urethra, vaginal atresia, and a normal anus, bladder, and colon. Fetal chromosomes were normal, 46,XX.

DISCUSSION

Persistent cloaca and persistent urogenital sinus anomalies are caused by the abnormal growth and development of the urorectal septum [Allen and Husmann, 1991]. This septum divides the fetal cloaca into two compartments; the dorsal cloaca will form the rectum and the ventral cloaca will form the urogenital sinus. This is accomplished between the 5th and 8th week of development. Normal urinary and genital tract development depends on that of the urorectal septum [Allen and Husmann, 1991]. The varied presentations of urorectal septal defects (i.e., persistent urogenital sinus, persistent cloaca and their associated urinary, reproductive and lower gastrointestinal tract anomalies and communications, fistulous or complete) may reflect the effects of varied degrees of abnormal development of the urorectal septum or interruptions of the growth of the septum at varied time points between the 5th and the 8th week of development. We propose that the anomalies observed in our patient and her fetus, although somewhat different in presentation, represent different manifestations of the abnormal growth or development of the urorectal septum.

Allen and Husmann [1991] proposed that persistent cloaca and persistent urogenital sinus anomalies be referred to as urorectal septal defects rather than cloacal anomaly variants. We support this terminology as it accurately represents the developmental defect common to persistent cloaca and persistent urogenital sinus anomalies. Furthermore, the use of this terminology clearly distinguishes urorectal septal defects from cloacal exstrophy anomalies, which result from a defect in development of the cloacal membrane and the subumbilical ventral abdominal wall [Jeffs, 1987].

The cause of urorectal septal defects is currently unknown. Cocaine exposure in utero has been found to be associated with a variety of urogenital anomalies [Kain et al., 1992], including a report suggesting that a cloacal anomaly in a female originated as a secondary consequence of vasoconstriction of the uterine and fetal circulation [Greenfield et al., 1991]. A number of reports have demonstrated familial recurrence of exstrophy anomalies [Smith et al., 1992; Shapiro et al., 1984], including two cousins with bladder exstrophy and a mother and son with bladder exstrophy [Messelink et al., 1993]. Additionally, there have been a number of reports of monozygotic twins concordant for cloacal exstrophy [reviewed by Chitrit et al., 1993]. Discordance for cloacal exstrophy in monozygotic twins has also been reported [Langer et al., 1992]. Together, these reports suggest a genetic cause or multifactorial predisposition for exstrophy anomalies. The recurrence risk is generally considered to be between 1:70 [Messelink, 1993; Shapiro et al., 1984] and 1:100 [Carter, 1984]. To the best of our knowledge, this report is the first demonstrating inheritance of a urorectal septal defect. Statistically, it is very unlikely (1 in 2.5×10^9 odds) that the urorectal septal defects in the index-case and her fetus were random, unrelated occurrences. We propose that a genetic or multifactorial etiology be considered for this rare defect.

While the developmental defect in patients with urorectal septal defects is considered distinct from that of patients with exstrophy anomalies, the underlying cause of each has yet to be determined. As similar spinal cord and column anomalies have been associated

with urorectal septal defects [Hendren, 1992; Allen and Husmann, 1991] and exstrophies [McLaughlin et al., 1995; Warf et al., 1993], these may represent different manifestations of a broader, regional defect in embryological development. Warf et al. [1993] suggested that the relationship between cloacal and spinal anomalies may lie in the spacial relationship of the developing notochord and the cloaca. They outlined several theories as to how the development of these systems could affect each other; none, however, have been substantiated experimentally. Hartwig et al. [1990] hypothesized that malformations of the cloaca, abdominal wall and spinal cord result from a disturbance of the cell deposition process in the caudal end of the fetus. Escobar et al. [1987] hypothesized that the failure of the urorectal septum to meet and fuse with the cloacal membrane results in the persistence of the cloacal membrane and the abnormal differentiation of the external genitalia. The persistence or delay in the rupture of the cloacal membrane has been hypothesized to result in the different exstrophy anomalies, depending on the timing of the rupture of the membrane [Mildenberger et al., 1988; Marshall and Muecke, 1966]. In light of these theories, we hypothesize that urorectal septal defects and exstrophy anomalies may represent different manifestations of the same embryological defect. Since the expression of a multifactorial condition can be influenced by fetal sex [Thompson et al., 1991], perhaps exstrophies and urorectal septal defects are related conditions in which males are more commonly affected with exstrophy anomalies, whereas females present with persistent cloaca or urogenital sinus anomalies. If so, the familial recurrence of exstrophy anomalies would support the hypothesis that urorectal septal defects have a genetic or multifactorial etiology. This would also imply that a woman with a repaired urorectal septal defect or a couple with an affected child might be at risk for having a daughter with a urorectal septal defect (i.e., persistent cloaca or persistent urogenital sinus) or a male or female child with an exstrophy anomaly.

We anticipate that with improved surgical techniques, women with urorectal septal defects will be presenting for genetic counseling, as they may be concerned about having similarly affected children. For these women and for couples who have had an affected child, a recurrence risk of up to 1% may be appropriate. Prenatal ultrasound examinations are indicated to monitor at-risk pregnancies as fetal structural abnormalities suggestive of persistent cloaca [Cilento et al., 1994; Shalev et al., 1986] and exstrophy defects [Langer, 1992] have been observed. A normal ultrasound examination would suggest that a fetus is unlikely to be affected with a severe exstrophy anomaly, but, would offer only limited reassurance that the fetus is not affected with a urorectal septal defect.

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